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**REMARKS**

Claims 33 - 82 are pending in the present application. Claims 41 - 53, 62 - 72 and 79 - 82 have been withdrawn from consideration. Claims 33, 54 and 73 have been amended, leaving Claims 33 - 40, 54 - 61, and 73 - 78 for consideration upon entry of the present Amendment.

Support for the amendments to Claims 33, 54, and 73 can be found in the Specification on Page 16, line 15.

No new matter has been introduced by these amendments. Reconsideration and allowance of the claims is respectfully requested in view of the above amendments and the following remarks.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 33 - 40, 54 - 61, and 73 - 78 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in relevant art that the inventors, at the time the applications was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

In making the rejection, the Examiner states "The specification as filed teaches by way of example specific antisense to EDG-1 and EDG-3...which target specific EDG-1 and EDG-3 genes from human..." (Paper 15, Page 3).

Claims 33, 54 and 73 have been amended to claim an antisense to human EDG-1 and/or EDG-3.

The Examiner further states "As argued previously, there is a high level of unpredictability in the antisense art for design of functional antisense absent the sequence structure of the target sequence and knowledge of suitable regions which are open to binding by a particular antisense sequence" (Paper 15, Page 4).

Claims 33, 54 and 73 have been amended to claim an antisense to human EDG-1 and/or EDG-3 wherein the antisense oligonucleotide includes the translation initiation site of

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the EDG receptor. As demonstrated in Example 12, antisense oligonucleotides to EDG-1 and EDG-3 inhibit the expression of the EDG-1 and EDG-3 genes. The antisense oligonucleotides used in Example 12 bind to sequences around the initiation codon. Thus, the initiation codon is accessible for binding by antisense oligonucleotides. Applicants submit that amended Claims 33, 54 and 73 are within the scope of the invention as disclosed in the Specification. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112 is requested.

Claim Rejections Under 35 U.S.C. § 102(b)

Claims 33 – 34, 54 – 55 and 73 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Goetzl et al. ("Goetzl"), Journal of Immunology. Applicants respectfully traverse this rejection.

Goetzl is directed to a study of the relationship between the EDG receptors and apoptosis using lysophosphatidic acid and sphingosine 1-phosphate. In particular, Goetzl utilizes primer pairs to detect the presence of EDG receptor mRNAs.

In making the rejection the Examiner states "Goetzl teach on page 2050, col. 1, 3rd para., nucleic acid primer sequences to EDG-1 and EDG-3 receptors" (Paper 15, Page 5). The Examiner further states "Since Goetzl teach compositions having nucleic acid sequences which bind and hybridize to the claimed target gene, EDG-1 and EDG-3, the claimed antisense are anticipated by Goetzl."

Independent Claims 33, 54 and 73 are directed to antisense oligonucleotides wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor. Applicants submit that none of the oligonucleotide primers disclosed in Goetzl fit this description.

The primer sequences of Goetzl have been compared to the sequences of the EDG receptor using the BLAST program available through NCBI. Exhibit 1 shows the mRNA sequence of EDG-1. Exhibit 2 shows the BLAST alignment of the EDG-1 mRNA and EDG-1 primer 1 of Goetzl. As is clearly shown, a good alignment is found between the primer and

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the EDG-1 mRNA at nucleotides 118-142. Alignment of the EDG-1 primer 1 sequence and the EDG-1 mRNA in Exhibit 1 page 2 shows that EDG-1 primer 1 corresponds in a sense orientation to nucleotides 118-142 in the 5' untranslated region of the EDG-1 mRNA. Thus, the Goetzl EDG-1 primer 1 is not an antisense oligonucleotide wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor.

Regarding the Goetzl EDG-1 primer 2, Exhibits 3 and 4 show attempts to align this primer in both a sense and an antisense orientation with the EDG-1 mRNA. No significant alignment is obtained in either a sense or an antisense orientation. It is unclear to applicants which EDG-1 sequences primer 2 is designed to bind. It is clear, however, that primer 2 is not an antisense oligonucleotide wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor.

Goetzl also discloses primers for the EDG-3 mRNA. Exhibit 5 shows the mRNA sequence of EDG-3. Exhibit 6 shows the BLAST alignment of the Goetzl EDG-3 primer 1 and the EDG-3 mRNA. As is clearly shown in Exhibit 5, Pages 1 and 2, EDG-3 primer 1 corresponds in a sense orientation to nucleotides 423-445 of the EDG-3 gene. This sequence is well within the coding region of EDG-3, as the ATG initiation codon is at position 1. Thus, the Goetzl EDG-3 primer 1 is not an antisense oligonucleotide wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor.

Regarding the Goetzl EDG-3 primer 2, Exhibit 6 shows the alignment of the antisense version of primer 2 with the EDG-3 mRNA. Primer 2 corresponds in an antisense orientation to nucleotides 1101-1123 of EDG-3. Thus, the Goetzl EDG-3 primer 2 is not an antisense oligonucleotide wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor.

To anticipate a claim, a reference must disclose each and every element of the claim. *Lewmar Marine v. Varient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Applicants submit that none of the EDG-1 or EDG-3 primers disclosed in Goetzl are antisense oligonucleotides wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor. Indeed, none of the Goetzl primers includes the ATG initiation codon of an EDG

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receptor gene, and only one of the three primers appears to be an antisense primer to the 3' end of the EDG-3 gene. Applicants submit that as there is at least one element of Instant independent Claims 33, 54 and 73 that is not disclosed by Goetzl, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 to Goetzl is requested.

Claims 33 - 35, 54 - 56 and 73 - 75 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by WO9918513/N\_Geneseq\_1101 database accession number AAX36573 to Erikson et al. ("Erikson"). Applicants traverse this rejection.

Erikson is directed to methods for detecting compounds that modulate the activity of an LPA receptor. Of particular relevance to the instant application, Erikson discloses on Page 30 sense and antisense primer pairs used to amplify the coding regions of EDG-1 and EDG-3.

In making the rejection, the Examiner states "WO9919513 teaches an oligonucleotide of 35 bases comprising bases 1-18 of both instant SEQ ID NO:1 and SEQ ID NO:2" (Paper 15, Page 5).

The primer sequences of Erikson have been compared to the sequences of the EDG-1 and EDG-3 mRNAs. As shown in Exhibit 8, SEQ ID NO:10 encompasses nucleotides 241-264 of the EDG-1 mRNA, including the initiation codon in a sense orientation. This oligonucleotide does not encompass instant SEQ ID NO:1 as instant SEQ ID NO:1 is an antisense oligonucleotide. As is known in the biochemical arts, sense and antisense oligonucleotides are chemically distinct compounds. SEQ ID NO:11 of Erikson is an antisense oligonucleotide that spans nucleotides 1369-1389 of the EDG-1 mRNA. As illustrated in Exhibit 8, Erikson SEQ ID NO:11 is not an antisense oligonucleotide that includes the translation initiation site of an EDG receptor. Erikson thus does not disclose an antisense oligonucleotide to EDG-1 wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor.

As with the primers to EDG-1, the Erikson primers to EDG-3 have been compared to the sequence of the EDG-3 mRNA. As shown in Exhibit 9, SEQ ID NO:12 of Erikson encompasses nucleotides 1-18 of the EDG-3 mRNA, including the initiation codon in a sense

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orientation. This oligonucleotide does not encompass SEQ ID NO:2 as SEQ ID NO:2 is an antisense oligonucleotide. As is known in the biochemical arts, sense and antisense oligonucleotides are chemically distinct compounds. SEQ ID NO:13 of Erikson is an antisense oligonucleotide that spans nucleotides 1115-137 of the EDG-3 mRNA. As illustrated in Exhibit 9, Erikson et al. SEQ ID NO:13 is not an antisense oligonucleotide that includes the translation initiation codon of an EDG receptor. Erikson thus does not disclose an antisense oligonucleotide to an EDG-3 receptor wherein the antisense oligonucleotide includes the translation initiation site of the EDG receptor.

Based on the evidence submitted in Exhibits 8 and 9, Applicants submit that Erikson does not disclose oligonucleotides that comprise SEQ ID NOs: 1 and 2. Further, Applicants submit that Erikson does not disclose antisense oligonucleotides wherein the antisense oligonucleotides include the translation initiation site of an EDG gene. The two primers of Erikson that include the translation initiation site are both sense primers, not antisense. Reconsideration and reversal of the rejection under 35 U.S.C. § 102 to Erikson is therefore respectfully requested.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 33 - 40, 54 - 61 and 73 - 78 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Goetzl and Erikson in view of either U.S. Patent No. 5,801,154 to Baracchini et al. ("Baracchini") or U.S. Patent No. 5,951,455 to Cowser ("Cowser"). Applicants respectfully traverse this rejection.

Baracchini discloses antisense oligonucleotides that inhibit the expression of multidrug resistance-associated protein. Baracchini further teaches various suitable modifications of the antisense oligonucleotides.

Cowser teaches antisense oligonucleotides that inhibit the expression of human G-alpha-11, a member of the Gq subfamily of G proteins. Cowser further teaches various modifications of the antisense oligonucleotides.

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In making the rejection, the Examiner states "Goetzl and WO0019513 are relied upon to teach oligonucleotide compositions having nucleic acid sequences which hybridize to EDG-1 and EDG-3...Baracchini and Cowser are both relied upon to teach design of antisense oligonucleotides to a known target gene and modifications of said antisense for improved function *in vitro*" (Paper 15, Page 7).

As described in detail above, neither Goetzl nor Erikson disclose antisense oligonucleotides to EDG-1 and/or EDG-3 that inhibit expression of an EDG receptor and wherein the antisense oligonucleotides include the translation initiation site of an EDG gene. None of the primers of Goetzl include the translation initiation site of an EDG gene. While SEQ ID NOs: 10 and 12 of Erikson include the translation initiation codon, neither primer is an antisense primer. Further, the Erikson primers are taught as primers for PCR amplification of EDG genes. As is known in the biochemistry art, PCR amplification requires a heating step to separate nucleic acid strands. Such a heating step could also melt at least some of the secondary structure of an mRNA. Thus, Erikson does not teach primers that necessarily bind to EDG mRNA under non-denaturing conditions. Erikson teaches sense primers that can be used to amplify the EDG-1 and EDG-3 mRNA under the conditions of a PCR reaction. As stated by the Examiner "there is a high level of unpredictability in the antisense art for design of functional antisense absent the sequence structure of the target sequence and knowledge of suitable regions which are open to binding by a particular antisense sequence" (Paper 15, Page 4). Applicants submit that Erikson teach sense primers that bind EDG-1 and EDG-3 under the conditions of a PCR reaction, but fail to teach antisense oligonucleotides that inhibit the expression of an EDG gene under "native" conditions. There is no teaching in Erikson that would suggest that the initiation codon of EDG-1 or EDG-3 would be available for binding an antisense oligonucleotide under native structural conditions. Applicants thus submit that there is no teaching in Goetzl or Erikson of antisense oligonucleotides to EDG-1 and EDG-3 that inhibit the expression of an EDG gene and wherein the antisense oligonucleotide includes the translation initiation codon. Further,

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there is no teaching in either Goetzl or Erikson to suggest that the translation initiation codon of EDG-1 or EDG-3 would be available for antisense oligonucleotide binding.

Baracchini and Cowser do not cure the defect. Both references are directed to antisense compositions to genes other than EDG genes. While both Baracchini and Cowser are directed to antisense compositions, neither provides any teaching to suggest that the initiation codon of the EDG genes would be available for antisense oligonucleotide binding. Neither reference provides teaching as to which regions of EDG-1 or EDG-3 would be suitable targets for antisense oligonucleotides.

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing a *prima facie* case of obviousness, i.e., that all elements of the invention are disclosed in the prior art; that the prior art relied upon, coupled with knowledge generally available in the art at the time of the invention, contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or combined references; and that the proposed modification of the prior art had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *In re Fin*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); *Amgen v. Chugai Pharmaceuticals Co.*, 927 U.S.P.Q.2d, 1016, 1023 (Fed. Cir. 1996).

Applicants submit that there is no motivation to combine the PCR primers of Goetzl or Erikson with the antisense techniques of Baracchini or Cowser to produce the instant invention. While Goetzl does teach antisense inhibition, as stated previously, Goetzl teaches the use of a full-length antisense EDG mRNA to inhibit EDG expression (see Page 2054, Figure 5). There is no teaching in Goetzl to suggest that the primers used to amplify the EDG genes would be suitable for the inhibition of EDG gene expression. There is no teaching in any of the cited references that would suggest to one of ordinary skill in the art which regions, including the region containing the initiation codon, of the EDG gene would be available for binding to an antisense oligonucleotide. Applicants submit that even if one of skill in the art were to attempt to design antisense oligonucleotides to an EDG receptor, there

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is no teaching in any of the references that would guide one to sequences including the initiation codon. Further, given the unpredictability in the antisense art referred to by the Examiner, even if one were to use primers such as the PCR primers of Goetzl and Erikson to inhibit gene expression, there is no expectation of success. As is well-known in the antisense art, particular sequences may be inaccessible to binding by antisense oligonucleotides either due to RNA structure or the presence of RNA binding proteins. Thus, even if one were motivated to combine the references, there is no expectation of success. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is therefore respectfully requested.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance is requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130 maintained by Applicants' attorneys.

Respectfully submitted,

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

A marked-up version of Claims 33, 54 and 73 follows:

33. (Amended/Marked-up) An antisense oligonucleotide, wherein the antisense oligonucleotide inhibits the expression of a nucleic acid molecule encoding a human EDG-1 receptor; and wherein the antisense oligonucleotide includes the translational initiation site of the EDG-1 receptor.

54. (Amended/Marked-up) An antisense oligonucleotide, wherein the antisense oligonucleotide inhibits the expression of a nucleic acid molecule encoding a human EDG-3 receptor; and wherein the antisense oligonucleotide includes the translational initiation site of the EDG-1 receptor.

73. (Amended/Marked-up) An antisense oligonucleotide, wherein the antisense oligonucleotide inhibits the expression of a nucleic acid molecule encoding a human EDG-1 or EDG-3 receptor; and wherein the antisense oligonucleotide includes the translational initiation site of the EDG-1 or EDG-3 receptor.